

The full TMDD model for simulation (same target concentration case)

```
$PROBLEM TMDD FULL MODEL IV DOSING
$INPUT C ID TIME AMT DV EVID MDV CMT TYPE WT AGE
$DATA FULLTMDDSSINGLEIVDOSE.CSV IGNORE=C
$SUBROUTINES ADVAN13 TOL=9
```

```
.....
```

\$MODEL

```
COMP(COMP1); free drug amount in the plasma (central compartment)
COMP(COMP2); free drug amount in the peripheral compartment
COMP(COMP3); free target concentration
COMP(COMP4); drug-target complex concentration
```

```
.....
```

\$PK

```
CL = THETA(1)*EXP(ETA(1))*(WT/70)**0.75
V1 = THETA(2)*EXP(ETA(2))*(WT/70)
Q = THETA(3)*EXP(ETA(3))*(WT/70)**0.75
V2 = THETA(4)*EXP(ETA(4))*(WT/70)
KEL = CL/V1
K12 = Q/V1
K21 = Q/V2
RMAX = THETA(5)*EXP(ETA(5))
KON = THETA(6)*EXP(ETA(6))
KOFF = THETA(7)*EXP(ETA(7))
KDEG = THETA(8)*EXP(ETA(8))
KINT = THETA(9)*EXP(ETA(9))
KSYN = RMAX*KDEG
```

```
.....
```

\$DES

```
DADT(1)= K21*A(2)-(KEL+K12)*A(1)-KON*A(1)*A(3)+KOFF*A(4)*V1
DADT(2)= K12*A(1)-K21*A(2)
DADT(3)= KSYN-KDEG*A(3)+KOFF*A(4)-KON*A(1)*A(3)/V1
DADT(4)= KON*A(1)*A(3)/V1-KOFF*A(4)-KINT*A(4)
```

```
.....
```

\$ERROR

```
IPRED=0
I1=0
I2=0
I3=0
```

```
IF(TYPE==1) THEN
I1=1
IPRED=A(1)/V1;
ENDIF
```

```
IF(TYPE==3) THEN
I2=1
IPRED=A(3);
ENDIF
```

```
IF(TYPE==4) THEN
I3=1
IPRED=A(4);
ENDIF
```

```
Y= IPRED*(1+EPS(1)*I1+EPS(2)*I2+EPS(3)*I3)
```

TAROCC=A(4)/(A(3)+A(4)); Target Occupancy

::

\$THETA

(0.1848 FIX); 1 CL
(2.8 FIX); 2 V1
(0.6384 FIX); 3 Q
(3.011 FIX); 4 V2
(1.74 FIX); 5 RMAX
(75.17 FIX); 6 Kon
(25.92 FIX); 7 Koff
(5.36 FIX); 8 KDEG
(4.37 FIX); 9 KINT

::

\$OMEGA

0 FIX ; 1 CL
0 FIX; 2 V1
0 FIX; 3 Q
0 FIX; 4 V2
0 FIX; 5 RMAX
0 FIX; 6 Kon
0 FIX; 7 Koff
0 FIX; 8 KDEG
0 FIX; 9 KINT

::

\$SIGMA

0 FIX
0 FIX
0 FIX

\$SIMULATION (2674474) ONLYSIMULATION SUBPROBLEMS=1

::
\$TABLE C ID TIME AMT IPRED DV TAROCC EVID MDV CMT TYPE WT AGE
NOPRINT FILE=SDTABFULLTMDDSSINGLEIVDOSE001

Michaelis-Menten approximation of the full TMDD model for simulation (same target concentration case)

```
$PROBLEM MM MODEL IV DOSING
$INPUT C ID TIME AMT DV EVID MDV CMT TYPE WT AGE
$DATA MMSINGLEIVDOSE.CSV IGNORE=C
$SUBROUTINES ADVAN13 TOL=9
```

```
.....
```

\$MODEL

COMP(COMP1); free drug amount in the plasma (central compartment)
COMP(COMP2); free drug amount in the peripheral compartment

```
.....
```

\$PK

```
CL = THETA(1)*EXP(ETA(1))*(WT/70)**0.75
V1 = THETA(2)*EXP(ETA(2))*(WT/70)
Q = THETA(3)*EXP(ETA(3))*(WT/70)**0.75
V2 = THETA(4)*EXP(ETA(4))*(WT/70)
KEL = CL/V1
K12 = Q/V1
K21 = Q/V2
RMAX = THETA(5)*EXP(ETA(5))
KON = THETA(6)*EXP(ETA(6))
KOFF = THETA(7)*EXP(ETA(7))
KDEG = THETA(8)*EXP(ETA(8))
KINT = THETA(9)*EXP(ETA(9))
KSYN = RMAX*KDEG
```

VMAX = RMAX*KINT

KM = (KINT+KOFF)/KON

S1=V1

```
.....
```

\$DES

```
DADT(1)= K21*A(2)-(KEL+K12)*A(1)-VMAX*A(1)/(KM+A(1)/S1)
DADT(2)= K12*A(1)-K21*A(2)
```

```
.....
```

\$ERROR

```
IPRED=A(1)/V1
Y= IPRED*(1+EPS(1))
IRES=IPRED-DV
```

```
.....
```

\$THETA

```
(0.1848 FIX); 1 CL
(2.8 FIX); 2 V1
(0.6384 FIX); 3 Q
(3.011 FIX); 4 V2
(1.74 FIX); 5 RMAX
(75.17 FIX); 6 Kon
(25.92 FIX); 7 Koff
(5.36 FIX); 8 KDEG
(4.37 FIX); 9 KINT
```

```
.....
```

\$OMEGA

```
0 FIX; 1 CL
0 FIX; 2 V1
```

```
0 FIX;      3 Q
0 FIX;      4 V2
0 FIX;      5 RMAX
0 FIX;      6 Kon
0 FIX;      7 Koff
0 FIX;      8 KDEG
0 FIX;      9 KINT
```

```
:::::::::::::::::::  
$SIGMA
```

```
0 FIX
```

```
$SIMULATION (2674474) ONLYSIMULATION SUBPROBLEMS=1
```

```
:::::::::::::::::::  
$TABLE C ID TIME AMT IPRED IRES DV EVID MDV CMT TYPE WT AGE  
NOPRINT FILE=SDTABMMSINGLEIVDOSE001
```